IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques Dumas et al. Examiner: Yong Soo Chong

Serial No.: 09/458,014 Group Art Unit: 1617

Filed: December 10, 1999 Confirmation No.: 8328

Title: INHBITION OF P38 KINASE USING ACTIVITY SUBSTITUTED HETEROCYCLIC UREAS

BRIEF ON APPEAL

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on 27 August 2009 and the Final Office Action dated 15 January 2008, please consider the following remarks.

The fee of $540.00 as set forth under § 41.20(b)(2) is being paid via EFS. The Commissioner is hereby authorized to charge any additional fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The present application is assigned to: Bayer Healthcare LLC by means of an assignment recorded on 27 July 2009 on Reel 023031 at frame 023031.

(ii) RELATED APPEALS AND INTERFERENCES

There are no pending appeals or interferences on subject matter directly related to this application.

(iii) STATUS OF CLAIMS

Claims 1-4, 8, 28, 30, 38, 44-45, 50-51, 55, 58 are pending in the present application.

Claims 5-7, 9-27, 29, 31-37, 39-43, 46-49, 52, 54, 56-57 have been cancelled.

Claim 53 has been withdrawn.

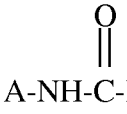
Claims 1-4, 8, 28, 30, 38, 44-45, 50-51, 55, 58 are on appeal.

(iv) STATUS OF AMENDMENTS

Appellants' amendment filed on 3 August 2009 canceling all claims except 45 and 58 was not entered. See the Advisory Action mailed 12 August 2009, item 7.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to a method for the treatment of rheumatoid arthritis, comprising administering a compound of formula I



I

wherein B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen

up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_2-C_{10} alkenyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is -O-, -S-, -N(R^5)-, -$(CH_2)_m$-, -C(O)-, -CH(OH)-, -$(CH_2)_m$O-, -$(CH_2)_m$S-, -$(CH_2)_m$N(R^5)-, -O$(CH_2)_m$-, -CHX^a, -$NR^5C(O)NR^5$ $R^{5'}$-, -$NR^5C(O)$-, -$C(O)NR^5$-, -CX^a_2-, -S-$(CH_2)_m$- and -N(R^5)$(CH_2)_m$-,

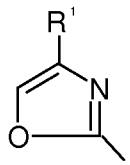
m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1},

wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, -CO_2R^5, -C(O)$NR^5R^{5'}$, -C(O)- NR^5, -NO_2, =O, -OR^5, - SR^5, - $NR^5R^{5'}$, -C(O)R^5, -SO_2R^5, -$SO_2NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, -CO_2R^5, -C(O)$R^{5'}$,-C(O)$NR^5R^{5'}$, =O, -OR^5, -SR^5, -NO_2, -$NR^5R^{5'}$, -$NR^5C(O)R^{5'}$, -$NR^5C(O)OR^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C-C_{10} heteroaryl, C_6-C_{14} aryl, C_4-C_{24} alkheteroaryl and C_7-C_{24} alkaryl

A is a heteroaryl moiety selected from the group consisting of



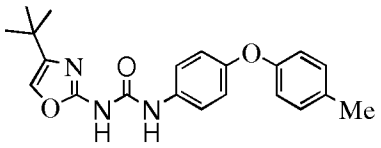
wherein

R^1 is selected from the group consisting of halogen, C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-

C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl.

See, for Example, independent claim 1, the specification on page 6 at line 22-23, and the specification on page 7 at line 19 to page 13, line 22.

The invention also relates to **a** method for the treatment of rheumatoid arthritis comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound of formula



. See, for example, independent claim 59, the election, compound 297 and the specification on page 102.

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds for rejection are presented for review on appeal:

1. Rejection of Claims 1-4, 8, 28, 30, 38, 44-45, 50-51, 55, 58 under 35 U.S.C. 112 first paragraph, as non-enabled.

2. Rejection of 1-4, 8, 28, 30, 44-45, 50-51, 55 under the doctrine of obviousness-type double patenting over claims 50-74 of copending Application No. 09/838,286; claims 1-16 of copending Application No. 09/947,761; claims 34-36, 39-42, 44 of copending Application No. 10/361,858; claims 1-13, 15-17, 20, 22-30 of copending Application No. 10/788,426; claims 1-69 of copending Application No. 10/848,567; claims 1-34, 37-41 of copending Application No. 11/932,548; and claims 1-16 of copending Application No. 12/181,032.

(vii) ARGUMENT

1. Rejection of Claims1-4, 8, 28, 30, 38, 44-45, 50-51, 55, 58 under 35 U.S.C. §112

Claims 1-4, 8, 28, 30, 38, 44-45, 50-51, 55, 58 stand rejected under 35 U.S.C. 112 first paragraph, as allegedly non-enabled. Appellants respectfully traverse this rejection.

The specification provides *objective* enablement for the methods of the present claims. In the Advisory Action, the Examiner asserts, " The claims encompass virtually every disease or disorder that is mediated by p38 kinase" and "inhibition of p38 is not well known in the field to be correlated to any particular disease." However, the claims are directed to a method of treating rheumatoid arthritis and not virtually every disease, as alleged. Moreover, as discussed below, inhibition of p38 is well known to be correlated with rheumatoid arthritis.

Objective enablement can be found throughout the specification. For example, page 103 provides an assay to determine the *in vitro* inhibitory properties of compounds of the present invention using a p38 kinase inhibition assay (and IC_{50} data). In addition, the *in vivo* inhibitory properties of a given compound can be determined using the murine LPS induced TNFα production *in vivo* model on page 104 of the specification. Furthermore, page 2 of Appellants specification provides a skilled worker with numerous clinical studies and references showing links between TNFα production and/or signaling and rheumatoid arthritis (See e.g., Maini. *J. Royal Coll. Physicians London* **1996**, *30*, 344). In addition, the specification provides a number of publications which have linked rheumatoid arthritis to excess or undesired matrix-destroying metalloprotease (MMP) activity. For example, on page 4 of the specification see, Woessner et al. *J. Biol. Chem.* **1984**, *259*, 3633, which deals with MMP and osteoarthritis. See also, Mullins et al. *Biochim. Biophys. Acta* **1983**, *695*, 117 which deals with MMP and rheumatoid arthritis. See also, Woolley et al. *Arthritis Rheum.* **1977**, *20*, 1231; Gravallese et al. *Arthritis Rheum.* **1991**, 34, 1076) and Williams et al. *Arthritis Rheum.* **1990**, *33*, 533, which deals with MMP and septic arthritis.

A skilled worker looking to the specification for additional guidance on what is known in the field would find that inhibitors of p38 are active in animal models of TNFα production, including a murine lipopolysaccharide (LPS) model of TNFα production and page five of the specification states:

> "Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Fruend's adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes."

The specification also indicates that because inhibition of p38 leads to inhibition of MMP production and inhibition of TNFα production, p38 inhibitors (such as those of formula I) will be useful in treatment of numerous diseases. In addition to the animal models discussed on page 103 and 104 of the application, the disclosure by Badger et al. JPET 279:1453-1461(1996) (Exhibit A), clearly shows the performance of a p38 kinase inhibitor in animal models of Arthritis (see Figs 3 and 6). Numerous patents issued prior to the December 1998 filing date of this application claim p38 inhibitors for the treatment of arthritis. See, for example, US 5,932,576 and US 5,945,418. Moreover, there are currently four TNF inhibitors which are FDA approved for the treatment of rheumatoid arthritis (i.e, Enbrel, Remicade, Cimzia and Humira). Enbrel was approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and juvenile rheumatoid arthritis prior to the December 1998 filing date of this application. Clearly the efficacy of TNFα inhibitors in treating particular diseases was well known in the art at the time of the December 1999 filing date. Thus, the Examiners allegation in the Advisory Action that " it is not well established in the field to correlate inhibition of p38 with treatment of disease" is unfounded. The Examiner has not presented any evidence that the teachings of Badger et al. are contrary to the state of the art. Nor has any evidence been presented to refute the findings or conclusions made in any of the publications cited in the specification. In addition, no evidence has been presented that any of the methods claimed would not be effective in treating rheumatoid arthritis. Only unsupported allegations and conclusions regarding the state of the art are provided.

In any event, the specification also otherwise provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of Formula I used in the claimed methods and how to administer these compositions in the treatment of rheumatoid arthritis (see, e.g., pages 24-29). The specification also provides dosage ranges for the various methods of administration (see, e.g., page 29). Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat rheumatoid arthritis.

Even absent the specification disclosures discussed above, the rejection is clearly deficient in general under controlling case law. The courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. See *In re Marzocchi*, supra. The final office action does not adequately address why rheumatoid arthritis, which is known to be mediated by p38, could not be treated by disrupting the p38-signaling pathway. Other than broad conclusory statements no such evidence or reason for doubting Appellant's' disclosure has been provided.

Additionally, "the [enablement] requirement is satisfied if, given what they [, those of ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the claimed invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Using the compounds of formula I in the claimed methods would be routine for those of ordinary skill in the art in view of Appellant's disclosure. Explicitly providing dedicated assays for rheumatoid arthritis is not necessary to enable the present claims. See, for example, *In re Howarth,* 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art."); *In re Gay*, 309 F.2d 769, 774, 135 U.S.P.Q 311 (CCPA 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be.")

The Advisory Action states:" the specification does not provide any experimentation of

any compounds in an accepted specific rheumatoid arthritis assay". There is no requirement that an applicant provide any working examples relating to the treatment of disease to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (Fed. Cir. 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses). Instead, as discussed earlier, there is no requirement for any examples. See, for example, *Marzocchi*, supra, stating that how "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to perform the methods claimed. Instead of relying on proper probative evidence, the rejection is improperly based on bare allegations and conclusions. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the use of the claimed methods without undue experimentation.

It is thus clear that one of ordinary skill in the art would not have to engage in undue experimentation to determine the scope of the claim, nor to make and use the invention. The test for undue experimentation was set forth in, e.g., *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). Despite the discussion in the Final Rejection, the "*Wands* Factors" clearly support enablement herein. With respect to the factors noted in the Final Rejection, it is important to note that a determination of undue experimentation must be considered on a *compound by compound* basis. The mere fact that a claim is broad does *not* mean that it is undue experimentation is required to determine enablement of the compounds therein, if it is not undue experimentation to determine enablement for *each* compound in the scope of the claim. See, for example, *In re Colianni*, 195 U.S.P.Q. 150 (CCPA 1977). One of ordinary skill in the art can easily determine, with the guidance provided by the specification, whether a compound of formula I is effective for the treatment of rheumatoid arthritis. Thus, the mere fact that many compounds must be tested is not dispositive of lack of utility.

It is thus respectfully submitted that the claims are fully enabled by the present

specification, and that the rejection should be reversed.

2. Rejection of claims 1-4, 8, 28, 30, 44-45, 50-51, 55 under the doctrine of obviousness-type double patenting over claims 50-74 of copending Application No. 09/838,286; claims 1-16 of copending Application No. 09/947,761; claims 34-36, 39-42, 44 of copending Application No. 10/361,858; claims 1-13, 15-17, 20, 22-30 of copending Application No. 10/788,426; claims 1-69 of copending Application No. 10/848,567; claims 1-34, 37-41 of copending Application No. 11/932,548; and claims 1-16 of copending Application No. 12/181,032.

Copending Application Nos. 09/838,286; 09/947,761 are now abandoned. With regards to claims 34-36, 39-42, 44 of Application No. 10/361,858 only claims 41-42 remain pending and they have been amended to depend from claims outside the scope of this rejection. Thus, the rejections with regards to Application Nos.09/838,286; 09/947,761; and 10/361,858 are now moot.

With regards to claims 1-13, 15-17, 20, 22-30 of copending Application No. 10/788,426; claims 1-69 of copending Application No. 10/848,567; claims 1-34, 37-41 of copending Application No. 11/932,548 and claims 1-16 of copending Application No. 12/181,032, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Appellants' maintain the rejections under the doctrine of obviousness type double patenting are premature since allowable subject matter has not been identified in this application. Furthermore, no allegation has been made that these applications contain claims to the elected subject matter, which is allegedly patentably distinct from the remaining subject matter claimed. The obviousness type double patenting rejection based on generic claims in these co-pending applications is inconsistent with the restriction requirement.

No fee is believed to be due with this response, however, the Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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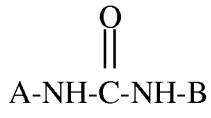
Date: **23 December 2009**

(xi) APPENDIX OF CLAIMS ON APPEAL

1. A method for the treatment of rheumatoid arthritis, comprising administering a compound of formula I



I

wherein B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_2-C_{10} alkenyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is -O-, -S-, $-N(R^5)$-, $-(CH_2)$-$_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$, $-NR^5C(O)NR^5\ R^{5'}$-, $-NR^5C(O)$-, $-C(O)NR^5$-, $-CX^a{}_2$-, $-S-(CH_2)_m$- and $-N(R^5)(CH_2)_m$-,

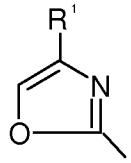
m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1},

wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)-NR^5$, $-NO_2$, =O, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-C(O)R^5$, $-SO_2R^5$, $-SO_2NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^{5'}$,$-C(O)NR^5R^{5'}$, =O, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C-C_{10} heteroaryl, C_6-C_{14} aryl, C_4-C_{24} alkheteroaryl and C_7-C_{24} alkaryl

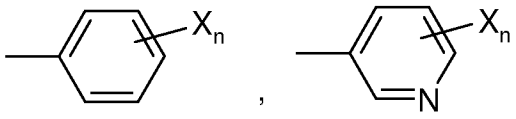
A is a heteroaryl moiety selected from the group consisting of

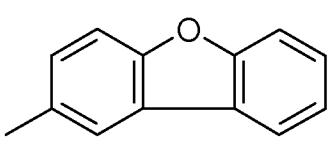


wherein

R^1 is selected from the group consisting of halogen, C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl.

2. A method as in claim 1, wherein B is up to a tricyclic aromatic ring structure selected from the group consisting of

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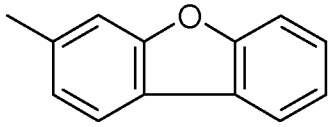
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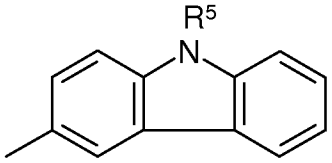
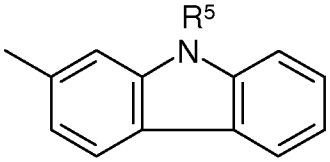

and

;

which is substituted or unsubstituted by halogen, up to per-halosubstitution, and

wherein n = 0-3 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_{1-10}-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, and substituted C_1-C_{10} alkyl, substituted C_{2-10}-alkenyl, substituted C_{1-10}-alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, NO_2, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

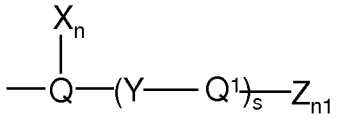
wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_{2-10}-alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is - O-, -S-, $-N(R^5)$-, $-(CH_2)$-$_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-NR^5C(O)NR^5R^{5'}$-, $-NR^5C(O)$-, $-C(O)NR^5$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$, $-CX^a_2$-, -S-$(CH_2)_m$- and $-N(R^5)(CH_2)_m$-,

m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halo and optionally substituted by Z_{n1}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, =O, $-SO_2R^5$, $-SO_2NR^5R^{5'}$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$,
$-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl; wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$,
$-C(O)NR^5R^{5'}$, =O, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C-C_{10} heteroaryl, C_6-C_{14} aryl, C_4-C_{24} alkheteroaryl and C_7-C_{24} alkaryl.

3. A method of claim 1, wherein B is



wherein Y is selected from the group consisting of –O-, -S-, $-CH_2$-, $-SCH_2$-, $-CH_2S$-, -CH(OH)-, -C(O)-, $-CX^a_2$, $-CX^aH$-, $-CH_2O$- and $-OCH_2$-, where X^a is halogen,

Q is a six member aromatic structure containing 0–2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution;

Q^1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution, and

X, Z, n and n1 are as defined in claim 1 and s is 0 or 1.

4. A method as in claim 3, wherein

Q is phenyl or pyridinyl, substituted or unsubstituted by halogen, up to per-

halosubstitution,

Q^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, or -Y-Q^1 is phthalimidinyl substituted or unsubstituted by halogen up to per-halo substitution, and

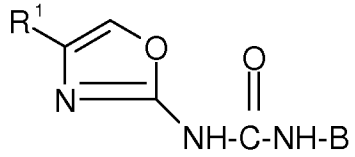
Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

8. A method as in claim 1, wherein R^1 is t-butyl.

28. A method as in claim 1, wherein the compound for formula I displays p38 IC_{50}'s of less than 10 μm as determined by an in-vitro p38 kinase inhibition assay.

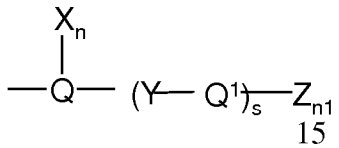
30. A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit p38.

38. A method as in claim 1 comprising administering a compound of the formula



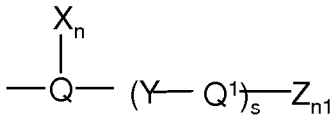
wherein R^1 is t-butyl and B are as defined in claim 1.

44. A method as in claim 1, wherein B is of the formula



wherein Q is phenyl or pyridinyl, optionally substituted by halogen up to per-halosubstitution, Q^1 is pyridinyl, phenyl or benzothiazolyl optionally substituted by halogen up to per-halosubstitution, Y is –O-, -S-, -CH_2S-, -SCH_2-, -CH_2O-, -OCH_2- or –CH_2-, X is C_1-C_4 alkyl or up to per-halosubstituted C_1-C_4 alkyl and Z is as defined in claim 1 , n = 0 or 1, s = 1 and n1 = 0-1.

45. A method as in claim 38, wherein B is of the formula



Q is phenyl or pyridinyl, optionally substituted by halogen up to per-halosubstitution, Q^1 is pyridinyl, phenyl or benzothiazolyl optionally substituted by halogen up to per-halosubstitution, Y is –O-, -S-, -C(O)- or –CH_2-, X is C_1-C_4 alkyl or up to per-halosubstituted C_1-C_4 alkyl and Z is as defined in claim 1 n = 0 or 1, s = 0 or 1 and n1 = 0 or 1.

50. A method as in claim 1, wherein B is

a) phenyl, pyridinyl, naphthyl, quinolinyl or isoquinolinyl, substituted by -Y-Ar and optionally substituted by

-halogen up to per-halosubstitution,

-C_1-C_4 alkyl,

-up to per-halosubstituted C_1-C_4 alkyl, or

- a combination thereof,

wherein Y and Ar are as defined in claim 1;

b) thienyl substituted by methyl; or

c) indolyl substituted by phenyl or pyridyl.

51. A method as in claim 1, wherein B is phenyl or pyridinyl substituted by -Y-Ar and optionally substituted by

-halogen ,up to per-halosubstitution,

-C_1-C_4 alkyl,

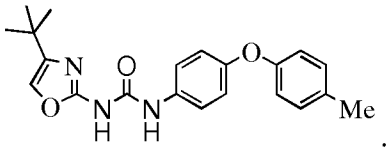
-up to per-halosubstituted C_1-C_4 alkyl, or

- a combination thereof,

wherein Y and Ar are as defined in claim 1.

55. A method according to claim 1, wherein R^1 is selected from the group consisting of halogen, C_3-C_{10} cycloalkyl, C_1-C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl.

58. A method for the treatment of rheumatoid arthritis comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound of formula



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(ix) EVIDENCE APPENDIX

Badger et al. JPET 279:1453-1461(1996) (Exhibit A)

(x) RELATED PROCEEDINGS APPENDIX

None